PATENT
Docket No.: **700157/46793**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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PATENT & TRADEMARK OFFICE
JC103

#15

Applicants	:	Fing et al.	Examiner: W. Sandals
Serial No.	:	09/269,321	
Filed	:	March 24, 1999	Art Unit: 1636
For	:	METHOD OF TARGETING MALIGNANT CELLS USING AN E2F RESPONSE PROMOTER	

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APPEAL BRIEF

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Pursuant to 37 CFR § 1.192, appellants hereby file their appeal brief in triplicate. Enclosed is the filing fee of **$160.00** required by 37 CFR § 1.17(c). The Commissioner is authorized to charge/credit Account No. 50-0850 for any deficiency/overcharge.

I. REAL PARTY IN INTEREST

Dana-Farber Cancer Institute, Inc. as assignee of U.S. Patent Application Serial No. 09/269,321, is the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences pertaining to the above-captioned application.

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III. STATUS OF CLAIMS

A. Claims 15-27 Are Finally Rejected

Pending claims 15-27 were finally rejected under 35 U.S.C. §112, first paragraph, as directed to subject matter which allegedly is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. Claims 15-27 were also rejected under 35 U.S.C. §112, first paragraph as directed to subject matter which allegedly is not enabled by the specification. In addition, claims 15-27 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 15, 25, and 26 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,885,833 ("the '833 patent"). Claims 15-23 and 25-26 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Raj et al., 1996 *Oncongene 12*:1279-1288 or Xiao et al., 1995 *Nature 375*:694-698 or the '833 patent in view of WO 94/18992 and U.S. Patent No. 5,529,774 ("the '774 patent").

IV. STATUS OF AMENDMENTS

Claims 1-14 were canceled and claims 15-17, 20 and 24 were amended, and claims 25 and 26 added in Appellants' Preliminary Amendment filed March 24, 1999.

The pending claims were amended and claim 27 added in an Amendment under 37 CFR § 1.111 filed on August 23, 2000.

No amendment after final has been filed.

V. SUMMARY OF INVENTION

Antineoplastic agents such as e.g., radiation and chemotherapeutic agents, are not highly selective. (Page 1) For example, neither radiation nor chemotherapeutic agents distinguish between malignant and non-malignant cells. (Page 1) Rather they target dividing cells over non-dividing cells. (Ibid). Unfortunately, quiescent malignant cells are not affected while normally dividing cells are adversely affected by these therapies. (Ibid).

The present invention overcomes this problem by using a vector system containing an E2F responsive promoter operably linked to a gene of interest (page 7). Malignant cells express high levels of "free" E2F, which, in turn, results in the E2F responsive promoter expressing the operably linked gene (page 8). As confirmed by the examples, the malignant cells had high levels of expression of the linked gene whereas the normal cells displayed virtually no such expression (pages 31-35, Figures 3-5). For example, as shown in Figure 5C, by injecting a vector system containing the tk gene into rat brains normal tissue toxicity was seen in the normal tissue versus extensive brain necrosis, inflammation and hemorrhage in the malignant tissues (Figure 5C and page 35). Thereby confirming the high selectivity *in vivo* between malignant and non-malignant cells. (Ibid). Preferably, the gene of interest encodes a cytotoxic or therapeutic protein. (Pages 14-15). These genes include suicide genes such as HSV tk and toxins (page 14).

VI. ISSUES

A. Whether claims 15-27 are properly rejected under 35 U.S.C. § 112, first paragraph, as directed to subject matter which is not supported by an adequate written description.

B. Whether claims 15-27 are properly rejected under 35 U.S.C. § 112, first paragraph, as directed to non-enabled subject matter.

C. Whether claims 15-27 are properly rejected under 35 U.S.C. §112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

D. Whether claims 15, 25, and 26 are properly rejected under 35 U.S.C. § 102(e) as anticipated by the '833 patent.

E. Whether claims 15-23 and 25-26 are properly rejected under 35 U.S.C. § 103(a) as unpatentable over Raj et al. or Xiao et al. or the '833 patent in view of WO/94/18992 and the '774 patent.

VII. GROUPING OF CLAIMS

All the claims are separately patentable. For example, even based upon the Examiner's rejection claims 15-27 are rejected under section 112, first and second paragraphs, only claims 15, 25, and 26 are rejected under section 102(e) as anticipated by the '833 patent, and only claims 15-23 and 25-26 are rejected over the combination of Raj et al. or Xiao et al. or the '833 patent in view of WO/94/18992 and the '774 patent.

VIII. ARGUMENT

A. The Rejection of Claims 15-27 under 35 U.S.C. § 112, First and Second Paragraphs Is Improper

1. The Subject Matter is Fully Supported

The Examiner has asserted that the phrases "encodes a protein that stimulates production" and "encodes a protein that inhibits production," which appear in claim 25, are not supported in the application as originally filed and as such, constitute new matter. Appellants respectfully submit that the Examiner's position is not supported in fact or law. The full phrase is that the "gene encodes a protein that stimulates production or expression of a cellular product, a positive potentiator."

> Page 14 of the specification recites the following:
>
> The E2F responsive promoter can be combined with a desired nucleic acid sequence encoding a heterologous gene such as one for a **positive potentiator** (such as a gene for a cytokine or a costimulating molecules, a gene for a missing or defective protein, (many cancers are believed to result in part from missing or defective proteins such as tumor suppressor genes e.g. retinoblastoma, p53, others from changes from a proto-oncogene such as ras, etc.)

As the above-quoted passage indicates, the phrase is specifically described. The claim specifies that such a gene is a positive potentiator --. The specification clearly teaches that these types of genes encode cytokines (which stimulate immune reactions), costimulating molecules (which also stimulates the immune system), genes for a missing or defective protein, etc. One skilled in the art therefore, at the time the application was filed, was thus explicitly taught that a

positive potentiator was one which stimulates production or expression of a cellular product, such as a cytokine, or a costimulating molecule.

Alternatively, in claim 25, the gene of interest is described as one "that inhibits production or expression of a cellular product, a negative potentiator." The specification at page 14 after describing positive potentiators, goes on to state that the gene is:

> a sequence for a **negative potentiator** (such as a toxin, an anti-sense RNA, a suicide gene such as HSV thymidine kinase (tk), a ribozyme, a dominant-negative mutant, an antibody such as an antibody with an intracellular localization signal, etc.... [Emphasis added]

Thus, the specification taught that such a negative potentiating gene was a toxin, an anti-sense RNA, a suicide gene such as HSV thymidine kinase (tk), a ribozyme, a dominant-negative mutant, an antibody such as an antibody with an intracellular localization signal, etc. Consequently, those skilled in the art knew that all these examples inhibit production or expression.

To comply with the description requirement, it is not necessary that the application describe the invention *ipsis verbis*. *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971). All that is required is that an ordinarily skilled artisan can recognize from the disclosure that applicants invented the subject matter of the claims, including the limitations recited therein. *In re: Smith*, 481 F. 2d, 910, 915, 178 USPQ 279, 284 (CCPA 1973). Exactly how the specification allows one skilled in the art to recognize that an applicant had possession of the claimed invention is not material. *In re Smith*, 481 F. 2d 910, 178 USPQ 279. The burden of showing that the claimed invention is not described in the specification rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not in *ipsis verbis* is insufficient. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Determining whether the written description requirement is met involves a factual inquiry insofar as determining how close the original description must come to the recitation in the claim(s). *See Eiselstein v. Frank*, 52 F.3d 1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995); *In re Driscoll*, 562 F.2d 1245, 1250, 195 USPQ2d 434,438 (CCPA 1977). Consequently, the disclosure reasonably conveys to the artisan the subject matter appearing in claim 25.

The Examiner has not met the burden imposed because as shown above, the skilled artisan would recognize from the disclosure, particularly at page 14, that applicants provided a written description of the subject matter of claim 25 (and claims dependent thereon), including the limitations recited therein.

Moreover, the basis of the Examiner's rejection does not apply to claims 20-24 and 27. These claims specify what the negative potentiator and positive potentiator are. For example, claim 20 states that the negative potentiator is a suicide gene, a dominant negative mutant or a cytotoxin. Claims 21-24 further specify particular negative potentiators. Claim 27 specifies particular positive potentiators. The rejection of claims 15-27 under 25 U.S.C. §112, second paragraph, is therefor improper and should be reversed.

2. The Subject Matter of Claims 15-26 Is Fully Enabled By the Specification

Claims 15-27 have been finally rejected under 35 U.S.C. § 112, first paragraph, as allegedly directed to subject matter which does not have enabling support in the specification. Although the Examiner acknowledges that the specification is "enabling for cells *in vitro*", it is contended that the claims are not "for cells in an animal, *in vivo*." (Final Office Action, page 3, paragraph 8). The Examiner further contends that "While applicants have shown examples of targeting a malignant cell *in vitro*, they have not demonstrated any method of targeting a malignant cell *in vivo*. In order to do so, undue experimentation is required." (Office Action, page 3, paragraph 8, lines 6-8, to page 4, line 1).

As Appellants explained in the amendment submitted on August 23, 2000, the specification is replete with *in vivo* data demonstrating a method of targeting a malignant cell *in vivo*. There are **three separate *in* vivo examples** (see pages 26-36 of the specification).

Applicants used the established rat glioma model and administered a marker gene, ß-galactosidase under control of an E2F responsive promoter and contrasted that with the gene under the control of the CMV promoter in both normal and malignant cells. As Figures 3 and 4 demonstrate, placement of the ß-gal gene under control of the CMV promoter resulted in expression in both normal and malignant tissues. In contrast, placement of the gene under the control of an E2F responsive promoter, the E2F promoter, resulted in extensive staining in malignant cells with virtually no staining in the normal tissues. *See* specification, pages 31-32,

Figures 3C and 3D. Administration of the marker gene under control of either the E2F or CMV promoter was performed by stereotaxic injection, a procedure which may be performed using standard neurosurgical procedures. *See* specification, page 13.

In a second example, the same vectors were injected into the femoral vein of rats forty eight hours after the rats underwent partial hepatectomy. Four days later, livers were harvested and stained for ß-gal activity, proliferating nuclear antigen (PCNA), and for the adenovirus fiber protein. The results showed selective expression in the liver malignant cells as opposed to the non-malignant cells. These results indicated that the high level E2F-1 promoter-mediated transgene expression *in vivo* is not a function of active cell cycling, but a result of the difference between the cells. (Specification, pages 32-33).

In a third example, vectors having the herpes thymidine kinase (tk) gene operably linked to the E2F-1 promoter or the CMV promoter were sterotatically injected into 7 day old intracerebral C6 gliomas, followed by systemic GCV treatment for one week. Administration of the gene under control of the E2F responsive promoter resulted in extensive areas of local brain necrosis, inflammation and hemorrhage. In contrast, the same gene under the control of E2F responsive promoter resulted in no obvious normal tissue toxicity. (Specification, pages 34-36).

Thus, assertions made by the Examiner which are a fundamental part of the rejection, are just wrong. There is extensive *in vivo* data establishing that the invention works as claimed.

The Examiner has also cited published references such as Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy," Marshall, E. (1995) *Science 269:*1050-1055, Verma et al. (1997) *Nature* 389:239-242, and Anderson, W.F. (1998) *Nature* 392:25-30. These references relate to clinical efficacy. That is not the standard that is to be used in the PTO. *In re Brana*, 51 F.3d 1560, 1568, 34 USPQ 2d 1437 (Fed. Cir. 1995). Reduction to practice of a patentable invention does not require that the invention be in a commercially satisfactory stage of development. *Scott v. Finney*, 34 F.3d 1058, 32 USPQ 2d 1115 (Fed. Cir. 1994).

Moreover, the Examiner's comments are not even applicable to claims such as claims 19-24, wherein the gene expressed is one that has a negative effect on a cell such as a cytotoxin.

Those genes are not intended for repeated administration or being present long-term. Claims 16 and 17 specify particular locations where the gene is to be used which Appellants demonstrate and exemplify in the specification.

Accordingly, in view of the above, Appellants respectfully submit that the Examiner has not met the burden required by the PTO and the case law for disputing the statements of enablement provided by the specification.

Applicants respectfully submit the claims are fully enabled by the specification. The specification teaches an appropriate promoter, E2F, and essential steps for selectively expressing a gene in a malignant cell, both *in vitro* and *in vivo*. Further, the specification teaches and confirms the use of different genes under the control of the E2F promoter for targeted expression in a malignant cell. Accordingly, the rejection of the claims under 35 U.S.C. § 112, first paragraph, as allegedly unsupported by the specification is in error and should be reversed.

3. Claims 15-27 Particularly Point Out and Distinctly Claim the Subject Matter Applicants Regard as the Invention

Claims 15-27 have been finally rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner objects to the phrases "selectively expressing the gene by the E2F in said cell" as it appears in line 12 of claim 25 and "negative potentiator" and "positive potentiator" in claims 19 and 25. According to the Examiner, "no mechanism for selective expression has been explicitly stated, and as such, is unclear as to the meaning of the term." (Final Office Action, page 6, paragraph 15). As discussed above, the specification clearly shows what is meant by selective expression - see the examples and the specification. For example, at page 7 Appellants teach:

> Vector systems containing an E2F responsive promoter operably linked to a gene of interest can be used to **selectively express** that gene in significantly higher levels in a malignant cell in contrast to a non-malignant cell. (Emphasis added).

Thus, considering claim 25 in its own terms, and particularly in light of the specification, the claim sets out and circumscribe a particular area with a reasonable degree of precision and particularity. The specification goes on at page 8 and states:

> Although not wishing to be bound by theory we believe that there is an excess of "free E2F, as well as loss of pRb/E2F repressor complexes in such cells, which results in the selective expression of for example the cytotoxic or therapeutic gene in the malignant cell...The E2F responsive promoter does not have to be the full length wild type promoter, but it must respond to a factor we believe to be E2F as determined by expression in a malignant cell having disruption of pRb function of a heterologous gene (sometimes referred to as a transgene) under the promoters control as opposed to a lack of expression in the presence of pRb/E2F complexes.

With respect to the phrases of "negative potentiator" and "positive potentiator", both of these terms are described in the specification at page 14. For example, a positive potentiator is exemplified by a gene for a cytokine, a costimulating molecule, a gene for a missing or defective protein, etc. Likewise, a negative potentiator might be a toxin, an anti-sense RNA, a suicide gene such as HSV thymidine kinase (tk), a ribozyme, a dominant-negative mutant, an antibody such as an antibody with an intracellular localization signal, etc. In addition, considering the claims in light of the prior art, as is permitted under *Moore*, both terms were known to skilled artisans at the time the application was originally filed. One skilled in the art therefore, at the time the application was filed, would recognize a positive potentiator as one which stimulates production or expression of a cellular product, such as a cytokine, or a costimulating molecule. One skilled in the art, at the time the application was filed, would also recognize a negative potentiator as one which inhibits production or expression of a cellular product. Moreover, claims 20-24 and 27 specify particular genes. Thus, the terms are explicitly defined in these claims.

The Examiner has also rejected claim 20 due to the term "dominant negative mutant" not being defined in the claims or the specification. This is a well-known term in the art. Thus, one skilled in the art would have known and understood the meaning of the term "dominant negative mutant." A patent need not teach *and preferably omits*, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) (emphasis added).

The rejection of claims 15-27 under 35 U.S.C. § 112 should be reversed.

B. The Rejection of Claims 15, 25, and 26 under 35 U.S.C. § 102(e) as Allegedly Anticipated by the '833 patent is Improper

In order for a publication to constitute an anticipation of an invention **every limitation** of the claim in issue **must be disclosed**, in that reference. *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 771, 218 USPQ 781, 789 (Fed. Cir. 1983), *cert denied,* 465 U.S. 1026, 104 S. Ct. 1284 (1984). Thus, there must be *no* differences between the subject matter of the claim and the disclosure of the prior art reference. The corollary of this rule is equally applicable. The absence from the reference of *any* claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986).

The '833 patent discusses nucleic acid constructs comprising an activator sequence, a promoter module comprising a nucleotide sequence which binds a protein of the E2F family, a nucleotide sequence that is a cell cycle homology region (CHR) and a structural gene.

It is respectfully submitted that there is no teaching or suggestion that the E2F promoter will also *selectively* direct expression in proliferating, *malignant* cells over normally dividing cells. Since the teachings of the '833 patent do not recognize Appellants' discovery that the E2F promoter may be used specifically to direct expression in dividing malignant cells, several aspects of Appellants' method as recited in Claims 15, 25, and 26 are also not taught by the '833 patent. This selective expression which has been demonstrated in three examples in the present application is all the more remarkable because E2F is normally expressed in a cell cycle dependent manner in normal cells as well as malignant cells (see paragraph bridging pages 7-9). Thus, based upon the '833 patent, one would have expected gene expression in normal cells.

Accordingly, there is no teaching for "[a] method of selectively expressing a gene in a malignant cell." Nor can there be any incidental inherency because there is no teaching in the '833 patent for step (a) of Appellants' claim 25, "determining whether a malignant cell expresses sufficient E2F to cause expression of a gene operably linked to an E2F responsive promoter." As such, under *Kalman* and *Kloster-Speedsteel*, because these claim limitations are nowhere taught in the '833 patent, claims 15, 25, and 26 cannot be anticipated by the '833 patent. The rejection of claims 15, 25, and 26 is therefore improper and should be reversed.

C. The Rejection of Claims 15-23 and 25-26 under 35 U.S.C. §103 as unpatentable over Raj et al. or Xiao et al. or the '833 patent in view of WO/94/18992 and the '774 patent is Improper

Appellants respectfully submit that one skilled in the art would not seek the teaching of Raj et al. or Xiao et al. or the '833 patent in view of WO 94/18992 and the '774 patent, in an effort to obtain the claimed invention. The Examiner has provided no convincing reason why such a combination would have been obvious to the skilled artisan to create a method of selective expression of a gene in a malignant cell. WO94/18992 and the '774 merely describe different vectors while Raj and Xiao and the '833 merely discuss E2F. There is no reason for putting them together.

Further, even if the references were combinable, such combination would not suggest the claimed invention. There is nothing in any of these references that suggests such a selective expression. Thus, there is no suggestion and no reasonable expectation of success in any of the cited references for selective expression in malignant cells of genes under the control of an E2F responsive promoter.

Indeed, WO94/18992 would suggest that it does not matter whether one gets selective expression or not.

The inventions of claims 19-24 and 27 are additionally patentable for the following reasons. Nothing in any of these references suggests that a positive potentiator such as a cytokine or costimulatory molecule (claim 25). Negative potentiators such as suicide genes (claims 19, 20 and 21), a cytotoxin (claims 19, 20 and 23), tk linked to an E2F promoter (claim 22), Domain III of *P. exotoxin A* (claim 24).

Accordingly, this rejection should be withdrawn.

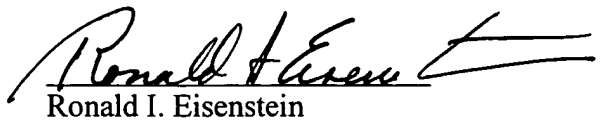
IX. CONCLUSION

For all of the foregoing reasons, it is submitted that the Examiner's final rejection of: claims 15-27 under 35 U.S.C. § 112, first and second paragraphs; claims 15, 25, and 26 under 35 U.S.C. § 102(e); and claims 15-23 and 25-26 under 35 U.S.C. § 103(a) is improper. It is,

therefore, respectfully requested that the Board reverse the Examiner's rejections and pass the application to issue.

Dated: November 9, 2001

Respectfully submitted,



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APPENDIX

15. The method of claim 25, wherein the nucleic acid cassette is present in a viral vector or nucleic acid delivery system.

16. The method of claim 25 wherein the malignant cell is a solid tumor.

17. The method of claim 16 wherein the solid tumor is a glioma.

18. The method of claim 17, wherein the nucleic acid cassette is present in a vector, wherein the vector is an adenovirus vector or a herpes virus vector.

19. The method of claim 16 wherein the nucleic acid sequence of interest encodes a negative potentiator.

20. The method of claim 19 wherein the gene of interest is a suicide gene, a dominant negative mutant or a cytotoxin.

21. The method of claim 20 wherein the gene of interest is a suicide gene.

22. The method of claim 21 wherein the suicide gene is HSV thymidine kinase.

23. The method of claim 20 wherein the gene of interest is a cytotoxin.

24. The method of claim 23, wherein the cytotoxin contains at least Domain III of *Pseudomonas extoxin A*.

25. A method of selectively expressing a gene in a malignant cell comprising:

(a) determining whether a malignant cell expresses sufficient E2F to cause expression of a gene operably linked to an E2F responsive promoter;

(b) adding an effective amount of a nucleic acid cassette to the malignant cell that was determined to express sufficient E2F, wherein said nucleic acid cassette comprises an E2F responsive promoter operably linked to a gene of interest, wherein said gene encodes a protein that stimulates production or expression of a cellular product, a positive potentiator or encodes a gene that inhibits production or expression of a cellular product, a negative potentiator;

(c) waiting until the nucleic acid cassette transduces the malignant cell; and

(d) selectively expressing the gene by the E2F in said malignant cell causing the E2F responsive promoter to express said gene.

26. The method of claim 25, wherein the E2F responsive promoter is selected from the group of promoters consisting of E2F1 promoter, dihydrofolate reductase promoter, DNA polymerase α promoter, c-myc promoter and ß-myb promoter.

27. The method of claim 25, wherein the gene of interest is selected from the group consisting of cytokines or costimulatory molecules.